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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,768	10/29/2001	Eric H. Baehrecke	4115-131	3246

23448 7590 12/11/2003

INTELLECTUAL PROPERTY / TECHNOLOGY LAW
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EXAMINER

DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 12/11/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/016,768

Applicant(s)

BAEHRECKE, ERIC H.

Examiner

MINH-TAM DAVIS

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-8, 13, 18 and 20-25 is/are pending in the application.
- 4a) Of the above claim(s) 6-8, 13, 18, 21 and 23-25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 20 and 22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4, 10. 6) ☐ Other: _____

DETAILED ACTION

Applicant's election with traverse of group 2, claims 1-5, 20, 22, SEQ ID NO:2, species "increases programmed cell death", in paper No:12 is acknowledged and entered.

Claims 1-8, 13, 18, 20-25 are pending in the instant application and Claims 6-8, 13, 18, 21, 23-25 have been withdrawn from further consideration by the Examiner under 37 CFR 1.142(b) as being drawn to non-elected invention.

Group 2, Claims 1-5, 20, 22, are currently under prosecution, wherein claims 1-5, 20, 22 are examined only to the extent of SEQ ID NO:1, 2 and 8.

The Drosophila amino acid sequence of SEQ ID NO:1 and the human amino acid sequence of SEQ ID NO:8 are rejoined with the human amino acid sequence SEQ ID NO:2, which is a fragment of SEQ ID NO:8.

Species increases programmed cell death is rejoined with species decreases programmed cell death.

It is noted that since claim 25 has been amended, claim 25 is rejoined with groups 92-98.

The traverse is on the following grounds:

1) The product claims and the method of using the products are not patentably distinct, because one having a method of using the instantly claimed polypeptides would obviously have to have the peptides to perform the method. The interdependence of the polypeptide product claims and the method of use thereof is confirmed by the requirement of 35 USC 112 to disclose different aspects of the invention in one

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application. Further, the court have recognized that it is in the public interest to permit an application to claim several aspects of his or her invention together in one application. Moreover, patents issuing on divisional applications which are filed to prosecute the claims that the Office held to be independent and distinct can be vulnerable to legal challenges alleging double patenting, and it is far from clear that the step of filing a terminal disclaimer is available to resolve a double patenting issue that arises after the issuance of patent on the divisional application. In addition, MPEP 821.04 recites that when elected product claims are found to recite patentable subject matter then all method claims for making and using the products may be rejoined and examined.

2) It is not an undue burden on the Office to search all six amino acid sequences through a BLAST program offered free on the Web. SEQ ID Nos: 1-5 are variants of each other, with some minor substitution, deletion, insertion and additions, however all possess the same apoptotic activity and have a conserved carboxy end region. Further, the Commissioner in 1996 waived the requirement of 37 CFR 1.141 and allow up to ten sequences to be examined in one application. His decision to waive the requirements of 37 CFR 1.141 was in response to a need in the biotechnology industry to protect its intellectual property without requirement the filing of 118 different applications, such as in this situation, while not creating an undue burden on the Office. Applicant requests that groups 1-6 are consolidated into a single group that includes SEQ ID NO:1-5 and 8 for unitary examination and further prosecution.

This is found not to be persuasive for the following reasons:

1) It is proper to restrict product from process of use of the product according to MPEP 806.05(h). The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. 806.05 (h)). In this instant case, a polypeptide could be used for several purposes, e.g. for biochemical assays, for making antibodies and for making affinity column to purify the antibodies.

Concerning rejoining product and method of use, The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise

proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

2) It is proper to restrict SEQ ID NO:1-5, because they are different domains of *Drosophila*, human, fish, mice and worms, respectively (figure 1 legend on p. 9), having distinct structure and require separate, non-coexisting searches. Therefore, it would be undue burden for the Examiner to search and examine all of groups 1-6 together.

Concerning the Commissioner statement, it is noted that although "up" to ten sequences can be examined in one application, there is no requirement that distinct sequences have to be examined in one application. Further, since searching more than one sequence would require separate searches, it would be undue burden for the Examiner to search and examine all of groups 1-6 together.

The requirement has been and is still deemed to be proper and therefore made FINAL.

After review and reconsideration, SEQ ID NO:8 is rejoined with SEQ ID NO:2, because SEQ ID NO:2 is a domain of the human E93 protein of SEQ ID NO:8. In addition, the Drosophila peptide of SEQ ID NO:1 is rejoined with SEQ ID NO:2 and SEQ ID NO:8.

Further, after review and reconsideration, It is noted that claim 4 is a generic linking claim, that links the inventions of SEQ ID Nos: 1-5 and 8.

The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claim 4. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Accordingly, group 2, claims 1-5, 20, 22, SEQ ID NOs:1, 2 and 8 are examined in the instant application. The Drosophila amino acid sequence of SEQ ID NO:1 and the human amino acid sequence of SEQ ID NO:8 are rejoined with the human amino acid

sequence SEQ ID NO:2, which is a fragment of SEQ ID NO:8. Species increases programmed cell death is rejoined with species decreases programmed cell death.

OBJECTION

Claims 1, 5 are objected to because part of claims 1, 5 are drawn to non-elected inventions, i.e. SEQ ID Nos: 3-5.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 20, 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 20 is indefinite, because claim 20 is confusing, due to the apparently typographical mistake for the language "and". It is not clear whether Applicant intends to claim : a) a polypeptide comprises SEQ ID NO:2 or variants thereof, or b) a polypeptide comprises SEQ ID NO:2 "and" variants thereof, wherein "and" could be reasonably interpreted as "conjugated with".

For the purpose of compact prosecution, it is assumed that claim 20 is drawn to a polypeptide that modulates programmed cell death, the polypeptide is selected from the group consisting of SEQ ID NO:2 and variants thereof.

2. Claim 22 is indefinite, because claim 22 is confusing, due to the apparently typographical mistake for the language "and". It is not clear whether Applicant intends to claim: a) the claimed polypeptide having SEQ ID NO:2 or variants thereof, or 2) the

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claimed polypeptide having SEQ ID NO:2 "and" variants thereof, wherein "and" could be reasonably interpreted as "conjugated with".

For the purpose of compact prosecution, it is assumed that claim 22 is drawn to an apoptotically active polypeptide selected from the group consisting of the amino acid sequence of SEQ ID NO:2 and variants thereof.

REJECTION UNDER 35 USC 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5, 20, 22 are rejected under 35 USC 101 because the claims are directed to non-statutory subject matter.

The polypeptide as claimed has the same characteristics and utility as a polypeptide found naturally and therefore do not constitute patentable subject matter. In the absence of the hand of man, the naturally occurring polypeptide is considered non-statutory subject matter. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Amendment of the claims to recite "an isolated polypeptide" is suggested to overcome this rejection.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE OF ENABLEMENT

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1. Claims 1-5, 20, 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO:8 that induce cell death, **does not reasonably provide enablement for a polypeptide that modulates "programmed cell death" or "apoptically active" polypeptide comprising SEQ ID NO:2 or SEQ ID NO:8 and variants thereof.** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-5, 20, 22 are drawn to:

1) A polypeptide that "modulates programmed cell death" comprising the amino acid sequence of SEQ ID NO:2 or 8,

2) An apoptically active polypeptide having at least 60% amino acid identity over the complete amino acid sequence of SEQ ID NO:1, wherein said polypeptide has the sequence of SEQ ID NO:2 or SEQ ID NO:8,

3) A polypeptide that "modulates programmed cell death", comprising SEQ ID NO:2 and variants thereof characterized by (a) at least 60% homology to SEQ ID NO:2, (b) a conserved carboxy end region having an amino acid sequence of amino acid residues 39 to 53 of SEQ ID NO:2 and (c) having apoptotic activity, and

4) An "apoptotically active" polypeptide having an amino acid sequence of SEQ ID NO:2, and variants having at least 90% homology to SEQ ID NO:2 and having "apoptotic activity".

The specification discloses that expression of full length hE93 gene which encodes the claimed polypeptide of SEQ ID NO:8 in human MCF-7 and 293T cell lines induces cell death, but not significant in the bovine cell line BHK (Example 2, Table 1 on page 43, and pages 42- 43). The specification also discloses that as control, expression of the proapoptotic protein Bax induces cell death of all three of the above cell lines and that expression of the antiapoptotic protein Bcl-xl also induces cell death in BHK and 293T cells (Example 2, Table 1 on page 43 and page 43).

The specification discloses that the Drosophila E93 binds to chromosomes and expression of the Drosophila E93 is sufficient to induce programmed cell death in different Drosophila cell types during development (p.10, last paragraph). The specification further discloses that the Drosophila E93 probably regulates programmed cell death by regulating the transcription of programmed cell death genes.

The specification also discloses that a 53 amino acid domain in Drosophila E93, SEQ ID NO:1, is conserved in human E93 fragment of SEQ ID NO:2, fish, mouse and the nematode E93 fragments of (SEQ ID NO:3-5, respectively (p.10, second paragraph, p.11 and figure 1). In figure 1 of the specification, residues 39-53 of the human E93 fragment of SEQ ID NO:2 is exactly the same as the corresponding amino acids 39-53 of the Drosophila E93 fragment of SEQ ID NO:1.

Although the specification discloses that SEQ ID NO:8 induces cell death, there is however no disclosure in the specification of any measurement of apoptosis or programmed cell death induced by SEQ ID NO:2 or 8.

Further, there is insufficient disclosure in the specification that the 53 amino acid domain of Drosophila E93 alone (SEQ ID NO:1), corresponding to the claimed human SEQ ID NO:2, is responsible for apoptosis or programmed cell death.

One cannot extrapolate the teaching in the specification to the claimed invention, because of the following reasons:

A. One cannot predict that cell death induced by the full length human SEQ ID NO:8 is apoptosis or programmed cell death, because there are three different types of cell death, based mainly on differences in the ultrastructural morphological features (Yuan, J et al, 2003, Neuron, 40: 404-413), and **one cannot predict which type of cell death is induced by SEQ ID NO:8**. Yuan et al teach that type 1 cell death, termed apoptosis, or programmed cell death, is characterized by cytoplasmic condensation, nuclear pyknosis, chromatin condensation, DNA fragmentation, cell rounding, membrane bebbing, cytoskeletal collapse, and the formation of membrane bound apoptotic bodies, and has as key players in the pathway, caspases, adaptor proteins such as Apf-1, and Bcl-2 family. Yuan et al further teach that type 2 cell death is characterized by the appearance of numerous cytoplasmic autophagic vacuoles of the lysosomal origin, and that type 3 cell death, similar to necrosis, is distinguished from the type 2 cell death by its lack of lysosomal involvement (Yuan et al, p.401-402). Similarly, Wyllie, AH et al, 1980, Internatl Rev cytology, 68: 251-306, teach that critical event leading to the development of necrosis is loss of cellular volume homeostasis, whereas apoptosis differs from necrosis in mechanism, wherein apoptotic cells do not show evidence of increased membrane permeability, at least until after the

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characteristic morphological changes have appeared (p.291, under Mechanism, and p.292-299). Thus without determining characteristics of cell death induced by SEQ ID NO:8, it is unpredictable that SEQ ID NO:8 modulates programmed cell death.

B. Further, based on protein homology, one cannot predict that the full length human E93 of SEQ ID NO:8 would have similar function as that of the full length Drosophila E93 of SEQ ID NO:10, such as inducing apoptosis or programmed cell death, nor that the human E93 fragment of SEQ ID NO:2 would have similar function as that of the Drosophila E93 fragment of SEQ ID NO:1, which is however not known.

It is noted that the claimed full length human E93 of SEQ ID NO:8 has 15% identity with the fly E93 of SEQ ID NO:10 (specification p.10, first and second paragraph), as shown by MPSRCH sequence similarity search (MPSRCH search report, 2003, us-10-016768a-8.res, pages 1-2). It is further noted that SEQ ID NO:2, a 53 amino acid fragment of human E93 of SEQ ID NO:8 has 9 amino acid difference with SEQ ID NO:1, a 53 amino acid fragment of the fly E93, as shown in figure 1 in the specification or 83% similarity.

It is clear that, although there is a 15% similarity between full length Drosophila E93 polypeptide and the full length human E93 of SEQ ID NO:8, and 83% similarity between the Drosophila E93 fragment of SEQ ID NO:1 and the human E93 fragment of SEQ ID NO:2, there is a 85% dissimilarity between SEQ ID NO:8 and the full length sequence of Drosophila E93 , and 17% dissimilarity between SEQ ID NO:1 and SEQ ID NO:2, respectively, and the effects of these dissimilarities upon protein structure and

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function cannot be predicted. Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Biol. 111:2129-2138, 1990) who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein.

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Clearly, with a 85% dissimilarity between SEQ ID NO:8 and the full length sequence of Drosophila E93 , and a 17% dissimilarity between SEQ ID NO:1 and SEQ ID NO:2, the function of the SEQ ID NO:8 or SEQ ID NO:2 polypeptide could not be predictably the same as full length Drosophila E93, or the Drosophila E93 fragment of SEQ ID NO:1, based on sequence similarity with Drosophila E93 or SEQ ID NO:1. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see

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legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter downregulated in adenoma . However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph).

Clearly, given not only the teachings of Bowie et al, Scott et al, Lazar et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 85% dissimilarity

between SEQ ID NO:8 and the full length sequence of Drosophila E93 , and a 17% dissimilarity between SEQ ID NO:1 and SEQ ID NO:2, the function of the SEQ ID NO:8 or SEQ ID NO:2 polypeptide could not be predicted, nor would it be expected to be the same as that of the full length sequence of Drosophila E93, or the Drosophila SEQ ID NO:1, based on sequence similarity with full length Drosophila E93 or fragment thereof of SEQ ID NO:1.

Further, the specification has not shown that the human peptide consisting of SEQ ID NO:2, which is a fragment of SEQ ID NO:8, or amino acids 39-53 of SEQ ID NO:2, nor that the Drosophila E93 peptide consisting of SEQ ID NO:1, which is a fragment of the full length Drosophila E93 polypeptide could induce cell death or apoptosis. One cannot predict however that the human peptide consisting of SEQ ID NO:2, which is a fragment of SEQ ID NO:8, and the Drosophila E93 peptide consisting of SEQ ID NO:1, which is a fragment of the full length Drosophila E93 polypeptide would induce apoptosis, since is well known in the art that not any fragment of a protein is responsible for the function of the protein, and that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein, as taught by Bowie et al, Burgess et al, Lazar et al, supra.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that

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information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the unpredictability of determining that SEQ ID NO:2 or variants thereof could modulate programmed cell death, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

2. If Applicant could overcome the above 112, first paragraph, claims 1-5, 20, 22 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO:8 that induces cell death, **does not reasonably provide enablement for a polypeptide that "modulates" programmed cell death or for an "apoptotically active" polypeptide.** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-5, 20, 22 are drawn to:

1) A polypeptide that "modulates programmed cell death" comprising the amino acid sequence of SEQ ID NO:2 or 8,

2) An "apoptotically active" polypeptide having at least 60% amino acid identity over the complete amino acid sequence of SEQ ID NO:1, wherein said polypeptide has a sequence of SEQ ID NO:2 or 8,

3) A polypeptide that "modulates programmed cell death", comprising SEQ ID NO:2 and variants thereof characterized by (a) at least 60% homology to SEQ ID NO:2, (b) a conserved carboxy end region having an amino acid residues 39-53 of SEQ ID NO:2 and (c) having apoptotic activity, and

4) An "apoptotically active" polypeptide having an amino acid sequence of SEQ ID NO:2, and variants having at least 90% homology to SEQ ID NO:2 and having "apoptotic activity".

The specification disclosure has been set forth above.

The specification further discloses that modulation can cause an increase or decrease in protein activity, binding characteristics or any other biological functional or immunological properties of the polypeptide (p.15, last paragraph bridging p.16).

It is noted that based on the definition of modulation in the specification on p.15, modulation of programmed cell death encompasses increasing or decreasing programmed cell death.

It is further noted that "apoptotically active" or having "apoptotic activity" encompasses increasing or decreasing apoptosis, since "apoptotically active" or "having apoptotic activity" could be positively or negatively apoptotically active or positive or negative apoptotic activity, in view that there is no definition of "apoptically active" or having "apoptotic activity" in the specification.

Claims 1- 5, 20, 22 thus encompass a polypeptide that could either “induce” or “inhibit” programmed cell death or apoptosis.

One cannot extrapolate the teaching in the specification to the scope of the claims. The specification only discloses that the full length human E93, SEQ ID NO:8, induces cell death. The specification and the claims do not disclose how to make an E93 polypeptide that could inhibit cell death, which has opposite effect of inducing cell death. It is unpredictable that SEQ ID NO:2 or 8 or variants thereof can inhibit programmed cell death, or apoptosis, because decreasing programmed cell death is a specific function, for example, requiring specific interaction with and/or controlling the activity of different cell death inhibitors (Oltvai et al, 1994, Cell, 79: 189-192), and not any protein would have said function.

In the absence of objective evidence or teaching of how to make SEQ ID NO:2 or 8 or variants thereof, that can inhibit programmed cell death, or apoptosis, and given the unpredictability of the ability of inhibition of apoptosis or programmed cell death by the claimed polypeptide of SEQ ID NO:2 or 8 or variants thereof, and further in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

3. If Applicant could overcome the above 112, first paragraph, claims 1-5, 20, 22 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the human E93 polypeptide of SEQ ID NO:8 that induces cell death *in vitro*, or full length Drosophila E93 comprising SEQ ID NO:1, **does not reasonably**

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provide enablement for a polypeptide “comprising” or “having” or “is” the sequence of SEQ ID NO:2 or variants of 60% identity to SEQ ID NO:1 or 2 or of 90% identity to SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-5, 20, 22 are drawn to:

- 1) A polypeptide that modulates programmed cell death “comprising” or “is” the amino acid sequence of SEQ ID NO:2 (claims 1-3),
- 2) An apoptotically active polypeptide having at least “60% amino acid identity” over the complete amino acid sequence of SEQ ID NO:1, wherein said polypeptide “has” the sequence of SEQ ID NO:2 (claims 4-5),
- 3) A polypeptide that modulates programmed cell death, comprising SEQ ID NO:2 and “variants” thereof characterized by (a) at least 60% homology to SEQ ID NO:2, (b) a conserved carboxy end region having an amino acid sequence of amino acid residues 39 to 53 of SEQ ID NO:2 and (c) having apoptotic activity (claim 20), and
- 4) An apoptotically active polypeptide having an amino acid sequence of SEQ ID NO:2, and “variants” having at least 90% homology to SEQ ID NO:2 and having “apoptotic activity” (claim 22).

The disclosure of the specification has been set forth above.

The specification further discloses that variants of SEQ ID NO:2 or 8 refers to an amino acid sequence that is altered by one or more amino acids, wherein the changes could be conservative or non-conservative (p.17, second paragraph). The specification

further discloses that guidance on which amino acids may be substituted, inserted or deleted without abolishing biological or immunological activity may be found using computer programs well known in the art such as DNASTAR software (p.17, second paragraph). The specification discloses various amino acids that could be modified, wherein the interchangeable amino acids have similar hydropathic index or score resulting in a polypeptide variant with similar biological activity (p.21, Item III, pages 22-23)

It is noted that the language "having" or "is" could be reasonably interpreted as an open language and is not the same as "consisting of". Therefore, for the purpose of compact examination, it is assumed that the terms "having" and "is" are commensurate in scope with the term "comprising".

It is noted that since SEQ ID NO:2 is a 53 amino acid fragment of the full length human E93 of SEQ ID NO:8, and since the apoptotic function of the fragment of SEQ ID NO:2 is unknown, *supra*, a polypeptide comprising or having or is SEQ ID NO:2 and variants thereof encompass unrelated sequences with unknown structure and function, which comprise SEQ ID NO:2 or variants thereof. Similarly, a polypeptide having at least 60% amino acid identity over the complete amino acid sequence of SEQ ID NO:1 encompasses variants of SEQ ID NO:1.

In other words, **the claims encompass numerous variants of the full length human E93 of SEQ ID NO:8, which comprises SEQ ID NO:2, or variants of the full length Drosophila E93, which comprises SEQ ID NO:1.**

Applicants have not shown how to make and use the claimed variants which are capable of functioning or have the biological properties of the full length polypeptide of SEQ ID NO:8, or of the full length Drosophila E93 as that which is being disclosed.

It is noted that it is only disclosed in the specification that SEQ ID NO:8 could cause cell death when transfected into human cell lines MCF-7 and 293 T (p.43), and that the full length Drosophila E93 could induce programmed cell death.

It is further noted that there is no indication that the claimed fragment of the human sequence of SEQ ID NO:2 or the Drosophila fragment consisting of SEQ ID NO:1 has any ability to induce cell death or apoptosis, because SEQ ID NO:2 is only a fragment of SEQ ID NO:8, and SEQ ID NO:1 is only a fragment of the full length fly E93 polypeptide, and it is well known in the art that not any fragment of a protein would confer the function of said protein, *supra*.

The claimed numerous variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the peptide, as well as insertions and deletions, provided that the change is not in the amino acid sequence fragment of SEQ ID NO:2. The specification and the claims do not place any limit on the type of substitution besides conservative substitution, nor the type of insertion or deletion. In addition, the specification and the claims do not place any limit on the number of amino acids that could be substituted or deleted or inserted in the sequences that comprise SEQ ID NO:2. Thus the scope of the claims includes numerous structural variants. Although the specification discloses that the types of changes are routinely done in the art, the specification and the claims do not provide

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sufficient guidance as to which type of substitution besides conservative substitution, or which amino acids could be deleted or inserted so that the claimed polypeptide could function as contemplated.

One cannot extrapolate the teaching in the specification to the scope claims because one cannot predict that the claimed numerous polypeptide sequences variants would have biological activity or properties related to that of SEQ ID NO:8, or the full length *Drosophila* E93, such as inducing cell death or having apoptotic activity. It is well known in the art that protein chemistry is probably one of the most unpredictable areas of biotechnology, as taught by Bowie et al, Burgess et al, Lazar et al, *supra*. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

Concerning the use of the DNASTAR software (p.17, second paragraph) disclosed in the specification for determining which various amino acids could be modified, wherein the interchangeable amino acids have similar hydropathic index or score could be used to produce a desired polypeptide variant, the specification has not disclosed which amino acids are identified by the DNASTAR program as the interchangeable amino acids such that the claimed variants would have the function of the polypeptide of SEQ ID NO:8. It is noted that the DNASTAR program only predicts protein function based on sequence similarity measure and direct primary sequence analysis, using methods to predict hydropathy, secondary structure, amphiplicity and antigenicity, or on the basis of sequence motifs (Plasterer, T, N, 2000, Mol Biotech, 16:

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117-125, see abstract). As discussed above, based on sequence similarity, even with similar hydropathy, one cannot predict the protein function, as taught by Bowie et al, Scott et al, Lazar et al and Burgess et al, *supra*. Further, there is no disclosure of any consensus sequence or motifs that are related to or responsible for the function of SEQ ID NO:8.

The specification does not disclose how to make the claimed polypeptide variants, such that they would function or have the properties as claimed, or how to use said polypeptide molecules if they did not have the function or properties claimed.

Given the unpredictability of protein chemistry, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

4. If Applicant could overcome the above 112, first paragraph, claims 1-5, 20, 22 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO:8 that induces cell death *in vitro*, **does not reasonably provide enablement for a polypeptide that modulates programmed cell death or having apoptotic activity "in vivo", as contemplated.** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-5, 20, 22 are drawn to:

1) A polypeptide that “modulates programmed cell death” comprising the amino acid sequence of SEQ ID NO:2 ,

2) An apoptotically active polypeptide having at least 60% amino acid identity over the complete amino acid sequence of SEQ ID NO:1, wherein said polypeptide has the sequence of SEQ ID NO:2 ,

3) A polypeptide that “modulates programmed cell death”, comprising SEQ ID NO:2 and variants thereof characterized by (a) at least 60% homology to SEQ ID NO:2, (b) a conserved carboxy end region having an amino acid sequence of amino acid residues 39 to 53 of SEQ ID NO:2 and (c) having apoptotic activity, and

4) An “apoptotically active” polypeptide having an amino acid sequence of SEQ ID NO:2, and variants having at least 90% homology to SEQ ID NO:2 and having “apoptotic activity”.

The specification disclosure has been set forth the above.

In addition, the specification contemplates treating various cancers by increasing the expression of SEQ ID NO:2 or 8 (p.40, first paragraph under “Therapeutics”).

Claims 1- 5, 20, 22 encompass a polypeptide of SEQ ID NO:2 or 8 or variants, that could have the intended use in modulating program cell death “in vivo” or have “in vivo” apoptotic activity such as in cancer cells.

One cannot extrapolate the teaching in the specification to the scope of the claims, because the enablement of the claimed invention appears to be based solely on in vitro data.

It is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in cell-cell interactions, and homeostasis. For example, it is well known in the art that the cellular concentration of members of Bcl-2 family is directly related to whether a cell will respond to an apoptotic signal, and that resistance of mature thymocytes to apoptotic signals correlates with high expression level of Bcl-2 protein, and overexpression of a cell death promoter BAD would counter the death inhibitory activity of Bcl-XL (Oltvai et al, 1994, Cell, 79: 189-192). Further, Gottschalk, AR et al, 1996, Cell Death and Differentiation, 3(1): 113-118, teach that overexpression of BAR, a well known apoptosis promoter, although can inhibit Bcl-2 from prolonging cell survival upon growth factor withdrawal, does not inhibit Bcl-XL from preventing apoptosis in a cell line WEHI-231. Gottschalk, AR et al further teach that regulation of a cell's apoptotic threshold is likely to result from a complex set of interactions among Bcl-2 family members and other, as yet uncharacterized, regulators of apoptosis. In addition, apoptosis is a complex phenomenon, wherein there are diverse cell death pathways, which depend on cell type and cell death stimulus (Vogel MW et al, 2002, Cerebellum, 1(4): 277-87) and apoptosis could be regulated by homeostasis mechanisms. For example, Xu Xin et al, 2001, FASEB J, 15(4): A313, teach that compensatory mechanism could regulate apoptosis to overcome the low induction of Fas and FasL in activated CD4⁺ cells of IRF-1 null mice. Further, Hummler E et al, 1994, PNAS, USA, 91: 5647-5661 teach that there is compensation within the CREB/ATF family of transcription factors, wherein mice with disruption of the CREB gene appear to be

healthy, and has an increase level of CREM, another member of the CREB/ATF family , and no change in the level of ATF1. Hummler E et al conclude that CREB is not the sole mediator of camp-dependent transcriptional regulation, and probably acts in concert with a specific subset of camp responsive element-binding proteins to transduce the camp signal and in its absence, these same protein can compensate for CREB function. Thus it is unpredictable that the induction of cell death by SEQ ID NO:8 would not be counteracted by the inhibitors of cell death, due to homeostasis.

Further, characteristics and responses of cultured cell lines generally differ significantly from the characteristics and responses of a primary tumor. Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactual antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic

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Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactual chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays. Further, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary - type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the

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contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Thus, based on the cell culture data presented in the specification, it could not be predicted that, in the *in vivo* environment, SEQ ID NO:2 or 8 would induce cell death in cancer cells.

In addition, it is unpredictable that the claimed compound could be useful for inducing cell death or apoptosis in cancer cells, due to possible inhibition by the overexpression in cancer patients of inhibitors of the effector caspases, enzymes necessary for the major apoptosis pathway. For example, Schimmer, AD, 2003, Cancer Res, 63(6): 1242-8 teach that cancer cells such as leukemia could overexpress endogenous inhibitors of the effector caspases, and block the caspase pathways.

Further, the claimed polypeptide of SEQ ID NO:8 or peptide of SEQ ID NO:2, and variants thereof must accomplish several tasks to be effective. It must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In addition the target cell must not have a alternate means of survival despite action at the proper site for the drug. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the assays, the claimed polypeptide is over-expressed in the cells by transfection of a vector expressing the polypeptide of SEQ ID NO:8 during the entire testing period. This is not the case *in vivo*, where exposure to the target site may be

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delayed or inadequate. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The polypeptide of SEQ ID NO:8 or the peptide of SEQ ID NO:2 may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life of the protein and the *in vitro* tests of record do not sufficiently duplicate the conditions which occur *in vivo*. In addition, the polypeptide of SEQ ID NO:8 or the peptide of SEQ ID NO:2 may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the peptide has no effect, circulation into the target area may be insufficient to carry the peptide and a large enough local concentration may not be established.

Thus there is no correlation between induction of cell death by SEQ ID NO:8 in transfected cells *in vitro* and induction of cell death or apoptosis *in vivo* by the claimed polypeptide of SEQ ID NO:2 or 8 in target cells such as cancer cells.

Given the unpredictability of induction of apoptosis or programmed cell death *in vivo* by the claimed polypeptide of SEQ ID NO:2 or 8 or variants thereof, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

REJECTION UNDER 35 USC 102(a)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 4 is rejected under 35 U.S.C. 102(a) as being anticipated by Adams MD, et al, Genbank Sequence Database (Accession Q9VD60), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, and Science 287: 2185-2195, publicly available on 24 March 2000, or Lee CY et al, August 2000, Molecular Cell, 6: 433-443, IDS # AG of paper No:4, on 01/30/02.

Claim 4 is drawn to an apoptotically active polypeptide having at least 60% amino acid identity over the complete amino acid sequence of SEQ ID NO:1.

1. Adams et al teach a sequence, SEQ ID NO:1165AA, which is 100% similar to SEQ ID NO:1 over the entire length of SEQ ID NO:1, under MPSRCH sequence similarity search (MPSRCH search report, 2003, us-10-016-768a-1.rsspt, p.1-2).

The sequence taught by Adams et al seems to be the same as the claimed sequence.

The reference does not specifically teach that the sequence is apoptotically

however, the claimed sequence appears to be the same as the prior art

the office does not have the facilities and resources to provide the factual

order to establish that the product of the prior art does not possess

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the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

2. Lee et al teach using a cDNA obtained from Baehrecke et al, 1995, the *Drosophila* E93 protein is expressed and detected in E93 transgene (p.440, second column, last paragraph, bridging p.441, first column). Lee et al further teach that E93 directs steroid-triggered programmed cell death.

The specification discloses that the *Drosophila* E93 gene was identified by Baehrecke et al, 1995, which however has a problem with gene sequencing, i.e. omission of one nucleotide, that changes the reading frame and encodes a different predicted protein (p.10, first paragraph). The specification further discloses that the correct *Drosophila* E93 nucleotide sequence encodes SEQ ID NO:10, which comprises the fragment consisting of SEQ ID NO:1 (p.10, second paragraph).

The detected *Drosophila* E93 protein taught by Lee et al encoded by a cDNA obtained from Baehrecke et al, 1995, which is inherently a correct sequence from a cDNA clone from Baehrecke et al, 1995, and has correct function of inducing programmed cell death, seems to be the same as the claimed sequence.

The reference does not specifically teach that the expressed E93 protein has at least 60% amino acid identity over the complete amino acid sequence of SEQ ID NO:1. However, the claimed sequence appears to be the same as the prior art sequence. The

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office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

REJECTION UNDER 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Baehrecke, EH et al, 1995, *Development Biol*, 171, 85-97, IDS#AB of paper No:4 on 01/30/02, in view of Sambrook et al, 1989 (*Molecular Cloning, A Laboratory Manual*,

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2nd Edition, Cold Spring Harbor Press, Cold Spring Harbor, p. 16.3-16.4), and Lee et al, supra.

Claim 4 is drawn to an apoptotically active polypeptide having at least 60% amino acid identity over the complete amino acid sequence of SEQ ID NO:1.

Baehrecke, EH et al teach isolation of the Drosophila E93 gene and its cDNA clone (p.89, second column, last paragraph, p. 90 and first paragraph of column 1 of p. 91)

Baehrecke, EH et al do not teach expression of the isolated cDNA clone. Baehrecke, EH et al do not teach that the Drosophila E93 protein is apoptotically active.

The specification discloses that the Drosophila E93 gene was identified by Baehrecke et al, 1995, which however has a problem with gene sequencing, i.e. omission of one nucleotide, that changes the reading frame and encodes a different predicted protein (p.10, first paragraph). The specification further discloses that the correct Drosophila E93 nucleotide sequence encodes SEQ ID NO:10, which comprises the fragment consisting of SEQ ID NO:1 (p.10, second paragraph).

Sambrook et al teach that cloned genes are conventionally expressed using expression vectors and that expression of cloned proteins have been used to: (1) confirm the identity of a cloned gene by using immunological or functional assays to detect the encoded protein; (2) produce large amounts of proteins of biological interest that are normally available in only limited quantities from natural sources; (3) to study the biosynthesis and intracellular transport of proteins following their expression in

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various cell types; and (4) to elucidate structure-function relationships by analyzing the properties of normal and mutant proteins (para bridging pages 16.3 and 16.4).

Lee et al teach that E93 directs steroid-triggered programmed cell death.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to express the cDNA clone of Baehrecke, EH et al with the methods of Sambrook et al, because Sambrook et al teach that cloned genes are conventionally expressed using expression vectors. One of ordinary skill in the art at the time the invention was made would have been motivated to combine the polynucleotide of Baehrecke, EH et al with the methods of Sambrook et al because Sambrook et al specifically teach that expressed cloned proteins are used to: (1) confirm the identity of a cloned gene by using immunological or functional assays to detect the encoded protein; (2) produce large amounts of proteins of biological interest that are normally available in only limited quantities from natural sources; (3) to study the biosynthesis and intracellular transport of proteins following their expression in various cell types; and (4) to elucidate structure-function relationships by analyzing the properties of normal and mutant proteins. One would have expected that the protein produced from the Drosophila E93 cDNA clone taught by Baehrecke, EH et al would be structurally the same as the claimed sequence, i.e. at least 60% similar to SEQ ID NO:1, which is a fragment of the full length Drosophila E93. One would have expected that the E93 protein produced from the cDNA clone taught by Baehrecke, EH et al with the methods of Sambrook et al would be apoptically active, since the Drosophila E93 protein can induce programmed cell death, as taught by Lee et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.



MINH TAM DAVIS

PATENT EXAMINER

October 31, 2003